

We Claim:

1. A controlled release pellet comprising:
  - a) an inert core that is water soluble or  
5 water swellable;
  - b) a drug layer applied to the inert core comprising:
    - i) a beta<sub>1</sub> adrenergic blocking agent, and
    - ii) optionally a binder;
  - c) a controlled release coating surrounding the  
10 drug layer.
2. A controlled release pellet as defined in Claim 1, wherein  
said beta<sub>1</sub> adrenergic blocking agent is metoprolol.
- 15 3. A controlled release pellet as defined in Claim 1, wherein  
the inert core has a diameter that is less than 30 mesh.
4. A controlled release pellet as defined in Claim 1, wherein  
the inert core has a diameter that is less than 40 mesh.  
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5. A controlled release pellet as defined in Claim 1,  
wherein the inert core has a diameter of about 30 to 200 mesh.
6. A controlled release pellet as defined in Claim 1, wherein  
25 the inert core has a diameter of about 40 to 120 mesh.
7. A controlled release pellet as defined in Claim 1,  
wherein the inert core has a diameter of about 60 to 80 mesh.
- 30 8. A controlled release pellet as defined in Claim 1,  
wherein the inert core is water soluble.

9. A controlled release pellet as defined in Claim 1,  
wherein the inert core is a sugar seed.

10. A controlled release pellet as defined in Claim 1,  
5 wherein the inert core is water swellable.

11. A controlled release pellet as defined in Claim 10,  
wherein the inert core is microcrystalline cellulose.

10 12. The controlled release pellet as defined in Claim 1,  
wherein the binder is selected from the group consisting of  
polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropyl  
cellulose, Hydroxypropyl methylcellulose, polyacrylate,  
ethylcellulose, or mixtures of the thereof.

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13. The controlled release pellet as defined in Claim 12,  
wherein the binder is hydroxypropyl methylcellulose.

14. The controlled release pellet as defined in Claim 1,  
20 wherein the drug layer further comprises a surfactant.

15. The controlled release pellet as defined in Claim 14,  
wherein the surfactant is selected from the group consisting  
of fatty acids, chelating agents, bile salts or mixtures  
25 thereof; capric acid, oleic acid and their monoglycerides,  
alkyl sulfates, sodium lauryl sulfate, sodium dodecyl sulfate,  
polysorbate 80, citric acid and phytic acid.

16. The controlled release pellet as defined in Claim 15,  
30 wherein the surfactant is polysorbate 80.

17. The controlled release pellet as defined in Claim 1,  
wherein the controlled release coating comprises a water  
insoluble or slightly water permeable polymer.

5       18. The controlled release pellet as defined in Claim 1,  
wherein the controlled release coating comprises a water  
insoluble film-forming polymer selected from the group  
consisting of cellulose acetate, cellulose acetate butyrate,  
ethyl cellulose, hydroxypropyl cellulose acetate,  
10      hydroxypropyl methylphthalate and cellulose acetate phthalate  
or mixtures thereof.

15      19. The controlled release pellet as defined in Claim 18,  
wherein the water insoluble film-forming polymer is cellulose  
acetate butyrate.

20      20. The controlled release pellet as defined in Claim 1,  
wherein the controlled release coating further comprises a  
channeling agent.

20      21. The controlled release pellet as defined in Claim 20,  
wherein the channeling agent is selected from the group  
consisting of sodium chloride, potassium chloride, sucrose,  
sorbitol, mannitol, polyethylene glycol, Eudragit<sup>®</sup> S100,  
25      propylene glycol, hydroxypropyl cellulose, hydroxypropyl  
methycellulose, hydroxypropyl methycellulose phthalate,  
cellulose acetate phthalate, polyvinyl alcohols, cellulose  
acetate butyrate, methacrylic acid copolymers, zein and  
mixtures thereof.

30      22. The controlled release pellet as defined in Claim 20,  
wherein said channeling agent is an enteric polymer.

23. The controlled release pellet as defined in Claim 22,  
wherein the channeling agent is a methacrylic acid copolymer.

5 24. The controlled release pellet as defined in Claim 1,  
wherein the controlled release coating further comprises an  
emulsifying agent.

10 25. The controlled release pellet as defined in Claim 24,  
wherein the emulsifier is selected from the group consisting  
of phospholipids, propylene glycol, polysorbates, poloxamer,  
glyceryl monostearate, other pharmaceutical emulsifiers or  
mixtures thereof.

15 26. The controlled release pellet as defined in Claim 24,  
wherein the emulsifier is a poloxamer.

20 27. The controlled release pellet as defined in Claim 1,  
wherein the controlled release coating further comprises a  
plasticizer.

25 28. The controlled release pellet as defined in Claim 27,  
wherein the plasticizer is selected from the group consisting  
of polyethylene glycol, propylene glycol, glycerol, triacetin,  
dimethyl phthalate, diethyl phthalate, dibutyl phthalate,  
dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl  
acetyl citrate, castor oil, poloxamer and varying percentages  
of acetylated monoglycerides.

30 29. An oral pharmaceutical tablet that comprises the  
controlled release pellet as defined in claim 2.

30. An oral pharmaceutical capsule that comprises the controlled release pellet as defined in claim 2.

31. The controlled release pellet defined in Claim 2 that  
5 exhibits the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm and 37°C in a phosphate buffer with a pH of 7.5,

0-40% of the metoprolol is released after 2 hours;

5-50% of the metoprolol is released after 4 hours;

10 25-80% of the metoprolol is released after 8 hours;  
not less than 50% of the metoprolol is released after  
16 hours.

32. The controlled release pellet defined in Claim 2 that  
15 exhibits the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm and 37°C in a phosphate buffer with a pH of 7.5,

0-25% of the metoprolol is released after 2 hours;

10-45% of the metoprolol is released after 4 hours;

20 35-75% of the metoprolol is released after 8 hours;  
not less than 75% of the metoprolol is released after  
16 hours.

33. The oral pharmaceutical tablet that is defined in Claim  
25 29 that further comprises an immediate release form of  
metoprolol.

34. The oral pharmaceutical capsule that is defined in Claim  
30 30 that further comprises an immediate release form of a  
30 metoprolol.

35. The oral pharmaceutical tablet as defined in Claim 33 that exhibits the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm and 37°C in a phosphate buffer with a pH of 7.5,

- 5        0-50% of the metoprolol is released after 2 hours;  
          10-60% of the metoprolol is released after 4 hours;  
          25-80% of the metoprolol is released after 8 hours;  
          not less than 50% of the metoprolol is released after  
          16 hours.

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36. The oral pharmaceutical tablet as defined in claim 33 that exhibits the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm and 37°C in a phosphate buffer with a pH of 7.5,

- 15      10-40% of the metoprolol is released after 2 hours;  
          20-50% of the metoprolol is released after 4 hours;  
          35-75% of the metoprolol is released after 8 hours;  
          not less than 60% of the metoprolol is released after  
          16 hours.

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37. The oral pharmaceutical capsule as defined in Claim 34 that exhibits the following dissolution profile when tested in a USP Type 2 apparatus at 75 rpm and 37°C in a phosphate buffer with a pH of 7.5,

- 25      0-50% of the metoprolol is released after 2 hours;  
          10-60% of the metoprolol is released after 4 hours;  
          25-80% of the metoprolol is released after 8 hours;  
          not less than 50% of the metoprolol is released after  
          16 hours.

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38. The oral pharmaceutical capsule as defined in Claim 37 that exhibits the following dissolution profile when tested in

a USP Type 2 apparatus at 75 rpm and 37°C in a phosphate buffer with a pH of 7.5,

10-40% of the metoprolol is released after 2 hours;

20-50% of the metoprolol is released after 4 hours;

5 35-75% of the metoprolol is released after 8 hours;

not less than 60% of the metoprolol is released after  
16 hours.

39. The pharmaceutical tablet as defined in Claim 33 that  
10 exhibits a peak plasma level between 3 and 8 hours after  
administration.

40. The pharmaceutical tablet as defined in Claim 39 that  
exhibits a peak plasma level between about 4.5 hours to about  
15 7.5 hours after administration.

41. The pharmaceutical capsule as defined in Claim 34 that  
exhibits a peak plasma level between 3 and 8 hours after  
administration.

20 42. The pharmaceutical capsule as defined in Claim 41 that  
exhibits a peak plasma level between about 4.5 hours to about  
7.5 hours after administration.

25 43. The pharmaceutical tablet as defined in Claim 33 that  
exhibits a  $C_{max}$  of less than 300 ng/ml.

44. The pharmaceutical tablet as defined in Claim 43 that  
exhibits a  $C_{max}$  of less than 275 ng/ml.

30 45. The pharmaceutical tablet as defined in Claim 44 that  
exhibits a  $C_{max}$  of between 200 ng/ml and 275 ng/ml.

46. The pharmaceutical capsule as defined in Claim 34 that exhibits a  $C_{max}$  of less than 300 ng/ml.

5 47. The pharmaceutical capsule as defined in Claim 46 that exhibits a  $C_{max}$  of less than 275 ng/ml.

48. The pharmaceutical capsule as defined in Claim 47 that exhibits a  $C_{max}$  of between 200 ng/ml and 275 ng/ml.

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49. A controlled release pellet consisting essentially of:

- a) an inert core that is water soluble or water swellable;
- b) a drug layer applied to the inert core comprising:
  - i) a beta<sub>1</sub> adrenergic blocking agent;
  - ii) a binder; and
  - iii) optionally a surfactant;
- c) a controlled release coating surrounding the drug layer comprising:
  - i) a water insoluble film forming polymer;
  - ii) a channeling agent; and
  - iii) optionally an emulsifier.

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50. A controlled release pellet as defined in Claim 49, wherein said beta<sub>1</sub> adrenergic blocking agent is metoprolol.

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51. A controlled release pellet as defined in Claim 49, wherein the inert core has a diameter that is less than 30 mesh.

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52. A controlled release pellet as defined in Claim 49, wherein the inert core has a diameter that is less than 40 mesh.

5 53. A controlled release pellet as defined in Claim 49, wherein the inert core has a diameter of about 30 to 200 mesh.

54. A controlled release pellet as defined in Claim 49, wherein the inert core has a diameter of about 40 to 120 mesh.

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55. A controlled release pellet as defined in Claim 49, wherein the inert core has a diameter of about 60 to 80 mesh.

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56. A controlled release pellet as defined in Claim 49, wherein the inert core is water soluble.

57. A controlled release pellet as defined in Claim 49, wherein the inert core is a sugar seed.

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58. A controlled release pellet as defined in Claim 49, wherein the inert core is water swellable.

59. A controlled release pellet as defined in Claim 49, wherein the inert core is microcrystalline cellulose.

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60. An oral pharmaceutical tablet that comprises the controlled release pellet as defined in claim 50.

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61. An oral pharmaceutical capsule that comprises the controlled release pellet as defined in claim 50.

62. The oral pharmaceutical tablet that is defined in claim  
60 that further comprises an immediate release form of  
metoprolol.

5 63. The oral pharmaceutical capsule that is defined in claim  
61 that further comprises an immediate release form of  
metoprolol.

64. A process for preparing a controlled release beta<sub>1</sub>  
10 adrenergic blocking agent pellet comprising:

- a) dissolving or suspending a beta<sub>1</sub> adrenergic blocking agent in an aqueous medium;
- b) applying the aqueous medium with the dissolved or suspended metoprolol onto a water soluble or water swellable inert core to create a drug layer on the inert core;
- c) applying a controlled release coating to the drug layer.

20 65. A process according to claim 64, wherein said beta<sub>1</sub> adrenergic blocking agent is metoprolol.